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## Non-invasive vascular measurements in diabetes mellitus and dyslipidemia.

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## Summary

### *Introduction*

The scope of this thesis is the application of non-invasive vascular measurements in two conditions characterised by prevalent vascular disease, diabetes mellitus and dyslipidemia. Functional vascular abnormalities are found very early in both diabetes mellitus and dyslipidemia, but it may take decades before clinical manifestations become apparent, and even then, in only part of these patients. Metabolic data, like glycemic or lipidemic history and status, provide limited predictive power for the risk of clinical vascular disease in an individual patient. Genetic characteristics may have some additive predictive value in future, but monitoring of the functional and structural vascular condition may yet be the most feasible tool to predict the risk for clinical events and form the best guide for interventions. It may also give direct information on the pathophysiology of vascular disease.

This thesis shows that a classical non-invasive vascular method, ankle pressure measurement, is insufficient to monitor the effects of an intervention (chapter 5). Another non-invasive vascular measurement method, the intima-media thickness (IMT), has been extensively used for this purpose in lipid-lowering studies, and is reviewed in chapter 7 and 8. In chapter 6 the effects on the IMT are compared of initial and long-term lipid-lowering therapy in dyslipidemia. The IMT method is also used to detect early structural vascular abnormalities in patients with glycogen storage disease Ia, expected to be particularly prone to cardiovascular disease (chapter 9). The IMT may serve as a mirror of the final common pathway of atherosclerosis of large arteries, but provides little insight in pathophysiologic changes. To this end, in chapters 2-4, a new bio-impedance method is used to compare various properties of an upper arm vascular bed, as blood volume, compliance and distensibility, in diabetic patients and control subjects. Apart from changes in arterial compliance and distensibility, the method also illustrates venous abnormalities in diabetes. Several results fit the hemodynamic angiopathic hypothesis. One of the studies also provides preliminary results on the predictive value of some vascular parameters in developing long-term vascular complications.

### *Diabetes mellitus*

Since the pathogenesis and epidemiology of micro- and macrovascular complications in type 1 (insulin-dependent) and 2 (insulin-independent) diabetes are different, (sub)clinical vascular changes were compared in both types of diabetes, as described in **chapter 2**. Parameters of the whole vascular bed of the upper arm were simultaneously assessed by our bio-impedance method in 53 type 1 and 28 type 2 diabetic patients, as well as in 33 healthy control subjects. Diabetic complications were divided into micro- and macrovascular. The systolic blood pressure and pulse pressure were elevated in all diabetic patients compared with the control subjects. The maximum compliance and distensibility of the large arteries were decreased in type 2 compared with type 1 diabetes and the control subjects. The distensibility of the total arterial bed was increased in type 2 diabetes



compared with the control subjects. These vascular changes in type 2 diabetes, despite conventional treatment, fit the hemodynamic angiopathic hypothesis. After a follow-up period, ranging from 4.5 to 7 years, progression of microvascular disease was found in 30 and 25% and of macrovascular disease in 25 and 43% of the patients with type 1 and 2 diabetes, respectively. For both type 1 and 2 diabetes, different vascular parameters were of predictive value in developing diabetic complications. Apart from generally accepted risk predictors like conventionally measured blood pressure and pulse pressure, maximum arterial compliance seemed to be important as such an indicator in type 1 diabetes, and blood volume of the large arteries and the cuff pressure at which the veins start to refill in type 2 diabetes.

In **chapter 3**, our first cross-sectional observation in type 1 diabetes is described, concerning the possible relation between diabetes associated changes in cortisol metabolism and volume homeostasis, and their relation to metabolic control. The cortisol to cortisone metabolite ratio reflects the overall direction of cortisol to its inactive metabolite cortisone interconversion, catalysed by  $11\beta$ -hydroxysteroid dehydrogenase ( $11\beta$ HSD). By measuring various plasma and urinary steroids and metabolites, changes in  $11\beta$ HSD activity can be assessed. In 8 normo- and microalbuminuric type 1 diabetic patients and 8 healthy control subjects, cortisol metabolism was evaluated and total blood volume assessed using our bio-impedance measurement. In both diabetic groups, urinary excretion of steroid metabolites was lower compared with the control group. Both the cortisol to cortisone metabolite ratio, and a parameter of  $5\alpha/5\beta$ -reduction of cortisol, were lower in the diabetic patients. In all combined diabetic subjects, most of these parameters were inversely correlated with diabetic control. Total blood volume of the upper arm was positively correlated with the cortisol to cortisone metabolite ratio in both the diabetic patients and the control subjects, with a leftward shift of the regression line in all diabetic participants. The cortisol to cortisone metabolite ratio decreased further after administering of an angiotensin-converting enzyme (ACE) inhibitor in 7 microalbuminuric diabetic patients. These data provide evidence for a disturbed balance of  $11\beta$ HSD and an impaired reduction of corticoids in type 1 diabetes. Notwithstanding the existing relation between total blood volume and the cortisol to cortisone metabolite ratio, the altered  $11\beta$ HSD activity cannot primarily be responsible for the sodium and fluid retention.

In the other cross-sectional observation in type 1 diabetes, described in **chapter 4**, blood volume distribution was evaluated. A supposedly impaired activity of endothelium-derived nitric oxide in type 1 diabetes, will cause an increased vascular tone in arteries. Considering the lower production of nitric oxide in veins than in arteries, an impaired activity would have less vasoconstrictive effects in veins. As the total plasma volume in diabetes is minimally changed, a redistribution of blood volumes from the arterial to the venous side of the circulation can be postulated. Therefore, in 16 normo- and microalbuminuric type 1 diabetic patients and 16 matched healthy control subjects, blood volumes, venous



myogenic response and arterial distensibilities were assessed in the upper arm using our electrical bio-impedance method. In diabetic patients the venous blood volume and venous myogenic response were increased whereas the arterial blood volume did not change. Moreover, in diabetic patients the distensibility of the large arteries was decreased, but an increase in distensibility was found of the total arterial bed. Therefore, the distensibility of the small arteries must have been increased. No differences were found between the normo- and microalbuminuric diabetic patients. These changes are in agreement with the expected shift of blood volume from the arterial to the venous side in type 1 diabetes, possibly related to an impaired activity or response of nitric oxide. Furthermore, they support the hemodynamic hypothesis of the pathogenesis of diabetic microangiopathy.

Walking training is an established conservative treatment for patients with intermittent claudication. The often distally localised obstructive lesions and microvascular disease in diabetes can complicate other (reconstructive) therapies, and probably walking training as well. In **chapter 5**, the results of a half-year supervised walking program in patients with limiting intermittent claudication and proven peripheral vascular disease are described. Walking parameters were determined in 33 (both type 1 and 2) diabetic patients and 136 control subjects every 2 months, while vascular parameters were obtained at the start and end of the program. Of the 33 diabetic patients, 25 (76%) completed the program, as did 87 of the 136 (64%) control subjects. After the training program, the symptom-free walking distance and the maximum walking distance were significantly increased in diabetic patients and in control subjects. The relative gain in maximum walking distance was 88% greater in the diabetic patients compared with the control subjects. The vascular parameters were comparable for both groups before and after the training. The greater relative gain of walking training in diabetes cannot be explained by the measured vascular parameters, so must be caused by other factors, like microcirculatory changes. These study results illustrate the inability of the classical ankle pressures to predict or monitor the clinical response.

### *Dyslipidemia*

After the demonstrated favourable effects of lipid-lowering therapy on the ultrasonographically measured IMT by several intervention trials, the effects of initial versus long-term lipid-lowering treatment on vascular wall characteristics were studied and are described in **chapter 6**. Patients with hypercholesterolemia ( $>6.5$  mmol/l) were retrospectively divided according to lipid-lowering therapy at baseline and treated during 1 year with the 3 hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors simva- or pravastatin to reduce total cholesterol below 5 mmol/l. At baseline no differences were found in biochemical and various vascular parameters between the 30 previously untreated ('initial') and the 54 already conventionally treated ('long-term') patients, except for triglycerides, which were higher in the initial group. After 1 year, the relative changes in lipid profile were significantly better in the initial- compared with the

long-term group. The relative changes in IMT of the mean internal carotid and common femoral arteries significantly differed between both groups, with a decrease in the initial- and an increase in the long-term group. After 1 year, in both groups, most other vascular wall characteristics were unaltered compared with baseline. As in both groups lipid profile was improved and no correlations could be found between the changes in lipid profile and IMT, other, including initial, effects of HMG-CoA reductase inhibitors than lipid-lowering alone must be involved in vascular changes.

The IMT of superficial large arteries is frequently used in intervention trials as 'surrogate endpoint' of cardiovascular disease. Studies concerning the influence of lipid-lowering, antihypertensive and some other therapies on the IMT of the carotid artery, are reviewed in **chapter 7**, and up-dated in **chapter 8**. After 1 year of lipid-lowering treatment, a reduced progression rate of the IMT was seen and aggressive lipid-lowering therapy proved to be more beneficial than conventional therapy. Little evidence supported a reduction of IMT progression in high-risk persons by antihypertensive drugs, like ACE inhibitors, beta-blockers and a calcium-channel blocker. No information was available about the effects on the IMT of combined lipid-lowering and antihypertensive treatment or homocysteine-lowering therapy. Intensified diabetes treatment did not seem to influence the IMT. Although some results were derived from substudies or secondary endpoint analyses, hormone replacement therapy had possibly beneficial effects on the IMT in contrast to antioxidant supplementation in high-risk individuals. The effects of non-pharmacological life style modification on IMT appeared to be promising. Since carotid IMT proved to be an independent cardiovascular risk predictor, it can be used as risk assessment in the individual patient. The range of treatment-induced changes in IMT does not support the use of IMT measurements in an individual patient to monitor treatment effects.

Deficiency of microsomal glucose-6-phosphatase leads to glycogen storage disease Ia (GSD Ia). Although more patients with GSD Ia reach adult age, no information is still available about the occurrence of cardiovascular disease in this condition, with persisting dyslipidemia and microalbuminuria despite dietary therapy. In **chapter 9**, our cross-sectional observation is described, which investigated whether GSD Ia was associated with premature cardiovascular changes. In 9 adolescent patients with GSD Ia and 9 matched healthy control subjects, lipid profile, non-invasive vascular measurements and echocardiography were performed. As expected, lipid profiles were significantly unfavourable in the patient compared with the control group. Seven patients with GSD Ia were treated with an ACE inhibitor because of (micro)albuminuria. Blood pressure was comparable in both groups. The IMT of the carotid and femoral arteries was comparable in both groups, with even significantly thinner values for some segments of the patients with GSD Ia. The relative myocardial wall thickness was significantly higher and the early to atrial filling ratio of the left ventricle lower in the patients with GSD Ia compared with the control subjects, fitting incipient cardiac remodeling and diastolic



dysfunction, respectively. After controlling for known cardiovascular risk factors in different multivariate models, GSD Ia remained an independent predictor for a thinner IMT and increase in relative myocardial thickness. Thus, despite the existence of longstanding dyslipidemia and microalbuminuria, GSD Ia is not associated with premature atherosclerosis.

## Conclusions

### *Diabetes*

#### *Bio-impedance measurement*

Diabetes mellitus, both type 1 and 2, is a condition with a wide range of known vascular abnormalities at various levels of the vascular tree. The bio-impedance technique allows us to collect some vascular characteristics, which cannot readily and/or simultaneously be obtained using other methods.

- The lower maximum compliance and large artery distensibility and higher distensibility of the total arterial bed in type 2 diabetes fit the hemodynamic angiopathic hypothesis. Vascular parameters of the upper arm, predicting long-term micro- and macrovascular complications, are different for type 1 (maximum arterial compliance) and type 2 diabetes (blood volume of the large arteries and the cuff pressure at which the veins start to refill).
- In type 1 diabetes, the  $11\beta$ HSD activity is altered and the reduction of corticoids impaired. Activity of  $11\beta$ HSD, reflected by the cortisol to cortisone metabolite ratio, is positively correlated with upper arm segmental blood volume, in both type 1 diabetic and nondiabetic participants, but cannot be primarily responsible for the sodium and fluid retention.
- In type 1 diabetes, the venous blood volume and venous myogenic response are increased, whereas the arterial blood volume remains unchanged. Because the distensibility is decreased of the large arteries, but increased of the total arterial bed and, therefore, of the smaller arteries, a redistribution of blood volume from the arterial towards the venous side can be postulated.

#### *Walking training*

Walking training is an effective treatment for intermittent claudication, with a greater relative gain in diabetic patients. Classical vascular characteristics did not predict the success of walking training, and did not change by the training program in correspondence with the changes in walking distances.

### *Dyslipidemia*

Dyslipidemia is a harmful condition for the vascular tree, by promoting atherosclerosis. IMT measurements allow detection of preclinical changes in the wall of large superficial arteries, like the carotid and femoral artery. Our review and application of this technique concerned conditions with possible or established atherosclerosis.

- After 1 year or more of lipid-lowering treatment a reduced progression rate of the carotid IMT has been seen in several intervention trials.
- Little evidence supports a reduction of the IMT progression rate by antihypertensive drugs. Still insufficient, but partly promising, evidence is found for the influence of other therapies on the carotid IMT.
- Measurement of the carotid IMT can be useful in the cardiovascular risk assessment of the individual patient, but not in monitoring treatment effects.
- Initiating lipid-lowering treatment with HMG-CoA reductase inhibitors has a more beneficial effect on the IMT progression than continuing already existing therapy, partly independent of the lipid-lowering effects.
- Glycogen storage disease Ia is associated with incipient cardiac remodeling and diastolic dysfunction but not with atherosclerosis, as detectable by IMT measurements, despite the existence of longstanding dyslipidemia and microalbuminuria.